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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BARNHART, LORA ELIZABETH	

ART UNIT	PAPER NUMBER
1651	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/627,739	MAOR, GILA	
	Examiner	Art Unit	
	Lora E. Barnhart	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7,9,11-103 and 108* is/are pending in the application.

4a) Of the above claim(s) *12,13,15,16 and 24-103* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7,9,11,14,17-23 and 108* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/15/08 has been entered.

Response to Amendments

Applicant's amendments filed 12/15/08 to claim 1 have been entered. Claims 6, 8, and 104-106 have been cancelled in this reply. No claims have been added in this reply. Claims 1-5, 7, 9, 11-103, and 108 remain pending in the current application, of which claims 1-5, 7, 9, 11, 14, 17-23, and 108 are being considered on their merits. Claims 12, 13, 15, 16, and 24-103 remain withdrawn from consideration at this time. References not included with this Office action can be found in a prior action. Any rejections of record not particularly addressed below are withdrawn in light of the claim amendments and applicant's comments.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 7, 9, 11, 14, 17-23, and 108 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of generating cultured chondrocytes that express type II collagen but not type I collagen by using one particular set of culture conditions, does not reasonably provide enablement for doing so using any given medium and culture conditions. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands*, 858 F.2d 731, 737, 8 USPQd 1400, 1404 (Fed. Cir. 1988) (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. While all of these factors are considered, a sufficient number are discussed below so as to create a *prima facie* case.

Claim 1 is broadly drawn to a method in which chondrocytes along with other cells are isolated from mandibular condyle tissue, plated initially as a monolayer, and then cultured under some undisclosed conditions for at least 7 days to yield chondrocytes that express type II, but not type I, collagen. The amendments to claim 1 are acknowledged, but it is noted that the only requirements made are that the initial plating be in monolayer and that the total culturing last at least 7 days. Claim 2 requires that the isolation step comprise some sort of selective process in which some non-

chondrocyte cell types are removed from the tissue and another selective process in which chondrocytes are isolated from the tissue. Claims 3-5 discuss the manner in which the condyle tissue is dissociated. Claims 7, 9, 11, and 17-22 describe the culturing conditions; it is noted that claims 7, 9, 11, and 17 describe the culture conditions in terms of what they do not include, rather than what they do include. Claims 23 and 108 describe the source of the chondrocytes.

Schnabel et al. (2002, *Osteoarthritis and Cartilage* 10: 62-70) teach that chondrocytes isolated from cartilage and cultured in monolayers using standard tissue culture techniques tend to dedifferentiate to a fibroblast-like state over time (page 62, column 2). Specifically, freshly isolated chondrocytes produce primarily type II collagen, but after a few weeks in monolayer culture, chondrocytes shift their expression pattern to the production of type I collagen (page 63, column 2, last paragraph; and page 67; it is noted that applicant has discussed this phenomenon in 5/15/08 reply, page 22, paragraph 1, e.g., and referred to various non-patent publications in support of the position, but no copies of these publications were furnished with the reply, so they could not be fully considered; copies have still not been provided). Schnabel indicates that the loss of type II collagen expression is a long-standing problem in the cartilage replacement art (pages 67 and 69).

Efforts have been made in the art to preserve the expression of collagen II in cultured chondrocytes. Cheung (1988, U.S. Patent 4,757,017) teaches a system in which articular chondrocytes are cultured on particles of hydroxyapatite in serum-supplemented media; in the system of Cheung, cultured chondrocytes retain their

expression of type II collagen for extended periods of time (Example 1 at column 5 et seq., especially column 9, lines 4-24; and column 3, lines 4-11). However, Cheung teaches that culturing on hydroxyapatite is essential to preventing dedifferentiation of the chondrocytes (column 9, lines 4-24). Given the teachings of the art, at the time of the invention, the skilled artisan would have reasonably expected that chondrocytes cultured in monolayers *in vitro* will eventually exchange expression of collagen II for that of collagen I.

The as-filed specification includes working examples in which mandibular condyles from neonatal mice are harvested and subjected to several rounds of enzymatic treatment: a first to free non-chondrocytes from the tissue, which are removed, and additional treatments to digest the remaining cartilage, yielding chondrocytes (page 43, line 29, through page 44, line 15). The resulting chondrocytes are cultured in DMEM supplemented with serum and ascorbic acid, β-glycerophosphate, calcium chloride, and pyruvate (hereafter "chondrocyte culturing medium"; page 44, lines 15-23). The specification indicates that after three days in chondrocyte culturing medium, the chondrocytes began to dedifferentiate, as marked by their production of type I collagen, but after 7 days, they appeared to redifferentiate to functional chondrocytes producing type II collagen (page 48, lines 5-29). Furthermore, applicants have supplied an affidavit under 37 C.F.R. 1.132 by inventor Maor (hereinafter "the Maor declaration") as to the correlation between the length of the culturing step and the collagen expression pattern in the chondrocytes (see also the appendix to applicant's reply of 12/15/08).

The scope of the single pertinent working example is insufficient to support the breadth of the instant claims. Schnabel and Cheung teach that generally, chondrocytes cultured without a scaffold (e.g. the hydroxyapatite of Cheung) dedifferentiate irreversibly in culture. Applicants have identified one culture media (the chondrocyte culturing medium) that may be used to produce type II collagen-producing chondrocytes. The instant claims do not materially limit the components of the culture media used for the method, because as discussed above, they primarily indicate what may **not** be present in the media. It is noted that claim 1 now requires that the cells be grown in a monolayer and that claims 7, 9, 11, 14, and 17 indicate a few components that may be absent from the culturing, but none of these claims places patentable limitations on the contents of the media. For example, claim 11 requires "conditions including a culture medium devoid of [various factors]," a limitation which encompasses conditions that do include those factors; see M.P.E.P. § 2111.03 regarding transitional phrases.

The working example indicates that both the components of the media are essential elements of the invention, given the teachings in the art that merely culturing chondrocytes in a monolayer (which is the scope of claim 1) would not yield type II collagen-producing chondrocytes. While a singular, narrow working embodiment cannot be a sole factor in determining enablement, its limited showing, in light of the unpredictable nature of the art as to identifying conditions in which chondrocytes can grow in monolayer culture and retain their expression of type II collagen and the lack of direction applicants present for all embodiments of the claims, provides additional

weight to the lack of enablement in consideration of the *Wands* factors as a whole. Thus, one of ordinary skill in the art would not have a reasonable expectation of success in using the claimed invention across its entire scope.

Applicant alleges that the novelty of the invention lies in the source of the chondrocytes (Reply, page 16, last paragraph et seq.). Applicant alleges that identifying chondrocyte culturing media would not have required undue experimentation (Reply, page 17, paragraphs 1 and 2). Applicant alleges that the age of the donor of the cartilage tissue is material to patentability (Reply, page 17, last paragraph). These arguments have been fully considered, but they are not persuasive.

The arguments regarding the importance of the source of the chondrocytes are merely the argument of counsel and are unsupported by evidence or declarations of those skilled in the art. Attorney argument is not evidence unless it is an admission, in which case, an examiner may use the admission in making a rejection. See M.P.E.P. § 2129 and § 2144.03 for a discussion of admissions as prior art. Counsel's arguments cannot take the place of objective evidence. *In re Schulze*, 145 USPQ 716 (CCPA 1965); *In re Cole*, 140 USPQ 230 (CCPA 1964); and especially *In re Langer*, 183 USPQ 288 (CCPA 1974). See M.P.E.P. § 716.01(c) for examples of attorney statements that are not evidence and that must be supported by an appropriate affidavit or declaration. Applicant has provided no comparative evidence to support the allegation that the selection of the tissue source is material to patentability.

Regarding the selection of culture conditions, the examiner has established the unpredictability of the state of the chondrocyte culturing art. Taken with the teachings of

Schnabel and Cheung, applicant's comments at page 17 merely serve to show that there was, at the time of the invention, a lack of consensus in the art as to the effects of various culture media components on chondrocytes. This lack of consensus is the reason for the enablement rejection, not a manner in which it can be overcome.

The examiner notes that applicant's arguments as a whole appear to allege that the claimed invention would have been obvious at the time of the invention. At page 17, paragraph 2, applicant explicitly states, "chondrocyte culturing media are known in the art and can be readily applied to the claimed teachings without undue experimentation." At this time, the examiner sees no basis for a *prima facie* finding of obviousness; however, repeated arguments by applicant that the conditions would have been routinely optimizable at the time of the invention may provide such a basis.

It is noted that only claim 23 addresses the age of the tissue from which the chondrocytes are obtained. In any case, once again, applicant has provided no relevant comparative data to be persuasive of error. Applicant's statement that "[n]umerous publications show that cells separated from mature cartilage undergo irreversible dedifferentiation resulting in type I producing cells" (Reply, page 17, last paragraph) is not supported by evidence, e.g., copies of these alleged publications or even citations of their relevant identifying information.

The Maor declaration has been fully considered, but given the claim amendments requiring a minimum of 7 days in culture, it is not clear that this declaration is probative regarding the patentability of the claims.

As a matter of form, applicant is cautioned against relying on open-source material that may be edited by the public (e.g., "Wikipedia," as at page 17, paragraph 1, of the reply). The content of such material is subject to change over time and is not necessarily subject to review by persons of ordinary skill in the art (as an article in a peer-reviewed scientific journal or a chapter from a textbook would be). Therefore, it is not generally considered a reliable source of quality information.

Claims 7 and 9 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 7 depends from claim 1 and requires that step (b) of claim 1, which necessarily yields cultured chondrocytes that express type II collagen but not type I collagen, be carried out using conditions devoid of a biomolecule-coated three-dimensional support. Claim 9 depends from claim 7.

There is no support, either implicit or explicit, for the requirement that the culturing step of claim 1 be carried out under conditions that lack any biomolecule-coated support. The specification appears to provide support for a method in which chondrocytes are plated on a tissue culture dish (which is certainly a "biomolecule-coated support" by the broadest reasonable interpretation of the term, since the dish's surface is covered – "coated" – in culture media, which contains biomolecules) in

monolayer culture and, over time, form multi-layered aggregates that express type II collagen; the specification does not provide support for a method in which chondrocytes are cultured in the absence of any biomolecule-coated support.

Applicant has provided no particular arguments that are pertinent to this rejection (see the reply at page 18, last paragraph). The examiner suspects that claim 7 exists to overcome prior art teachings in which chondrocytes are cultured on particles (e.g., Cheung's teaching of culturing chondrocytes on hydroxyapatite and tricalcium phosphate particles; see abstract of Cheung). However, the language of the claims is not commensurate in scope with these conditions.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 20 and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 20 does not appear to properly further limit claim 1. Claim 1 requires that the culturing step last for at least 7 days, but claim 20 allows that it may be as short as 5 days. Clarification is required.

Claim 23 requires that the tissue be "derived from a neonatal mammal," which is confusing because it is not clear whether this limitation excludes adult tissue. Adult mammals are necessarily "derived" from neonates. Clarification is required. If applicant intends to limit claim 23 to tissue isolated from a neonate, the claim should so indicate.

Claims 1-5, 7, 9, 11, 14, 17-23, and 108 are rejected under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter which applicant(s) regard as their invention. Evidence that these claims fail to correspond in scope with that which applicant regards as the invention can be found in the reply filed 12/15/08. In that paper, applicant has stated that the age of the donor whose cartilage tissue provides the chondrocytes for the method is material to patentability (page 17, last paragraph, through page 18, first paragraph), and this statement indicates that the invention is different from what is defined in the cited claims because they place no particular limit on the age of the donor. Claim 23 is included in this rejection because, as discussed above, the term "tissue derived from a neonatal mammal" reasonably includes tissue isolated from adult mammals.

No claims are allowed.

Applicant is requested to specifically point out the support for any amendments made to the disclosure in response to this Office action, including the claims (MPEP 714.02 and 2163.06). In doing so, applicant is requested to refer to pages and line numbers in the as-filed specification, **not** the published application. Due to the procedure outlined in MPEP § 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lora E. Barnhart whose telephone number is 571-272-1928. The examiner can normally be reached on Monday-Thursday, 9:00am - 5:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lora E Barnhart/
Primary Examiner, Art Unit 1651